REMARKS

This is in response to the office action dated July 28, 2003. Claims 2 and 3 have been amended. Claims 1 and 4-18 have been cancelled, without prejudice or disclaimer. New claims 19-25 have been added. In addition, the specification has been amended to insert numbered pages depicting Tables 1-5 which were included with the specification as originally filed.

Claim 2 has been amended to depend from a non-cancelled claim, and to recite an "L1 element comprising a sequence at least 95% similar to residues 1-884 of SEQ ID NO:1. This amendment is supported by original claim 2 and at, e.g., page 6, lines 25-31, and page 32-33, bridging paragraph.

Claim 3 has been amended to independent form, and to recite a method of identifying a candidate gene involved in systemic lupus erythematosus (SLE) comprising identifying a region of the genome adjacent to a disease-associated marker and selecting any gene containing an L1 element in an intronic region or in a 5' or 3' regulatory region as a candidate gene involved in SLE. This amendment is supported by the specification as filed at, *e.g.*, page 32-33, bridging paragraph, and page 34, lines 2-22.

New claims 19 , 20, and 21 are directed to specific embodiments of claim 2, *i.e.*, the L1 element being in an intronic region, in a 5' regulatory region, or in a 3' regulatory region, claims 19, 20 and 21, respectively. New claims 22 and 23 call for the L1 element having at least about 98% or 99% sequence similarity to nucleotides 1-884 of SEQ ID NO:1, claims 22 and 23, respectively. These claims are supported by the specification at, *e.g.*, page 34, lines 2-22. New claims 24 and 25 call for the distance between the first nucleotide of the L1 element and the first nucleotide of the gene being less than about 200,000 or less than about 100,000 base pairs, claims 24 and 25, respectively. These claims are supported by the specification at, e.g., page 34, lines 2-22.

No new matter has been added by this amendment. Each objection and rejection recited in the office action is discussed below.

Correction to the Specification

The Examiner required correction of Tables 1-5, submitted with the original specification as un-numbered pages. With this amendment, pages 74-104 have been submitted, which depict original Tables 1-5 on numbered pages. It is believed that this informality has thereby been corrected according to the Examiner's suggestion.

Indefiniteness

Claim 1-3 have been rejected as indefinite for not containing sufficient antecedent basis for various terms in claim 1. Claim 1 has now been cancelled, and claims 2 and 3 amended to provide correct antecedent basis for each term in the claims. Accordingly, it is believed that this rejection has been overcome.

Enablement

The Examiner has rejected claims 1-2 for alleged lack of enablement of any gene involved in any disease. Since claim 1 has been cancelled and claim 2 now depends from claim 3, it is believed that this rejection has been rendered moot.

The Examiner has also rejected claim 3 for alleged lack of enablement on the basis that "the specification has not established a clear correlation between any gene containing a full-length L1 element in their intronic region or containing a full-length L1 element with high sequence fidelity to the L1 consensus sequence in their 5' or 3' regulatory region and all complex diseases", that "no teaching of similarities or commonalities of a shared characteristic between the L1 elements capable of conferring complex disease exists", and that "the specification is silent to teachings of known markers of complex diseases" (Office Action, page 7). The Examiner also argues that "one cannot anticipate that every gene containing an L1 element will be involved in a complex disease", and that "in the absence of specific guidance as to how to identify other markers associated with complex diseases and furthermore their response to an L1 insertion it would require undue experimentation to identify the additional genes that may be involved with complex disease" (Office Action page 9).

The present invention defined by the claims as amended herewith is directed to a simple test to identify candidate genes involved in SLE. The Examiner's concerns, recited above, with respect to the alleged lack of correlation between any gene containing an L1 element and all complex diseases have thereby been alleviated. As described below, the identification of candidate genes in SLE is enabled by the present disclosure.

Further, the Examiner appears to be of the opinion that for the invention to be enabled, every gene containing an L1 element must be involved in a complex disease (Office Action, page 9). In this matter, the Examiner's attention is respectfully directed to MPEP 2164.08(b), stating "...typically, inoperative embodiments are excluded by the language in a claim (*e.g.*, preamble)...". Accordingly, the presence or identification of some genes not involved in SLE would not offend compliance with the enablement requirement, since the preamble calls for a candidate gene involved in SLE.

The Examiner further argues that "there is no guidance as to ... [a marker's] ... response to an L1 insertion" (Office Action, page 9), implying that this would necessarily mean undue experimentation to practice the invention. In support of this line of argument the Examiner cites Gilbert et al.(Cell 2002;110:315-325) as providing unpredictability because "little is known how L1 integration is completed", "an unexpected outcome ... is that L1 retrotranspositions can result in a variety of target site alterations", and L1 EN generates a sequence-specific endonucleolytic nick" etc., as well as Szak (Genome Biology 2002, volume 2), stating that "the precise determination of the boundaries of L1 elements is complicated" etc. (Office Action, page 10).

However, the teachings of the Gilbert and Szak references mean nothing to the present invention. In accordance with the amended claims, the present invention is drawn to a method to identify candidate genes involved in SLE comprising:

- identifying a region of the genome neighboring a disease-associated marker, and
- selecting any gene in the region containing an L1 element in an intronic region or in a 5' or 3' regulatory region as a candidate gene involved in SLE.

What mechanism is responsible for the presence of the L1 element, or, indeed, the specific boundaries of the L1 element, are of little consequence as the claimed method is not dependent on any such features. By contrast, the present invention is based upon Applicant's finding that (specification, page 4, lines 22-25):

> "... the proximity of an LINE element such as L1 to a region of the genome associated with the diagnosis of a complex disease or susceptibility to a complex disease can indicate the identity of the gene or genes involved in the pathogenesis of that disease".

Since the diagnosis of SLE as well as various SLE disease markers are well known in the art, and since the present specification provides ample guidance on how to identify L1 elements and their location in relation to a gene in a marker region, the specific mechanism by which the L1 element is inserted or, in fact, leads to the diagnosis, is of little relevance. Specifically, it has been established that "... it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." (*Newman v. Quigg* . . . (Fed. Cir. 1989); se also *Fromson v. Advance Offset Plate, Inc.* . . .(Fed Cir. 1983) ('[I]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.'). Nevertheless, however, the present specification discloses and discusses several potential mechanisms by which retrotransposon insertion of an L1 element could lead to a human disease such as SLE (specification at, *e.g.*, pages 29-32 and 41-42).

In addition, Applicants take issue with the Examiner's argumentation that there is no teaching as to similarities or commonalities of a shared characteristic between the L1 elements capable of conferring complex disease exists. As recited in the above excerpt from the specification, the location of the L1 element, *i.e.*, that the candidate gene contains an L1 element in an intronic region or in a 5' or 3' regulatory region, is an important feature of the invention which is also common to all claims. As to the characteristics of the L1 element itself, as used in the context of the present invention, these are described and defined at page 11, lines 2-21, and pages 32-34, and claims 2 and 22-25 set forth sequence and location characteristics common to L1 elements useful in various embodiments of the present invention.

What remains, then, is the Examiner's contention that the disclosure does not provide teachings of known markers of complex diseases or specific guidance as to how to identify other markers (Office Action, pages 7 and 9), and that "the specification fails to teach even the known disease markers with which their L1 elements could be correlated" (Office Action, page 11).

It is respectfully submitted that these contentions are in error. (As the present claims are directed to the use of a disease-associated marker of SLE, the following discussion pertains only to SLE markers). Contrary to the Examiner's contention, the specification does describe susceptibility loci or disease-associated markers for SLE and related L1 elements (see, *e.g.*, Table 1 and Fig. 2) and Examples 2-4 correlates these SLE susceptibility loci with the distance to an L1 element. Also, although the present invention is the first to correlate the markers with L1 elements, the level of skill and knowledge in the art is high in that several other SLE disease-associated markers are known as are methodologies for identifying them. As an example, enclosed with this response are 4 journal publications (Exhibits 1-4) published before the present application was filed, each describing the identification of one or more susceptibility loci for SLE. These references, as well as numerous other references published prior to the filing of this application, establish that the level of skill in the field of identification of susceptibility loci for SLE and other conditions was high at the time, and remains high. Further, as discussed above, U.S. case law has established that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. In the instant context, this means that not all SLE disease-associated markers must be associated with an L1 element for the invention to be enabled, since the presence or absence of an L1 element can be easily determined by a person of skill in the art.

Thus, claims 2-3 and 19-25 are fully enabled by the specification. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

Anticipation

Claims 1-2 stand rejected as allegedly anticipated by Kimberland et al. (Hum Mol Genet 1999;8:1557-1560, "Kimberland reference"). Specifically, the Examiner contends that Kimberland teaches a method to identify ß-globin and retinitis pigmentosa genes involved in a complex disease

by identifying a region neighboring a disease-associated marker, comparing the sequences of a 5' regulatory region or intronic region with an L1 consensus sequence, and identifying the ß-globin and retinitis pigmentosa genes (Office Action, page 4).

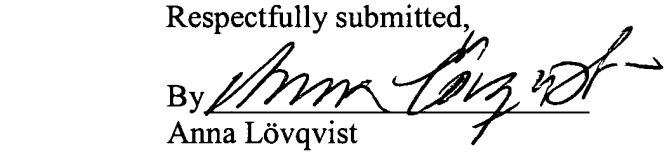
With this response, claim 1 has been cancelled and claim 2 now depends from claim 3. Thus, it is believed that this rejection has been rendered moot, and withdrawal of the rejection is respectfully solicited.

* * *

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: November 4, 2003

Respectfully submitted,

By 

Anna Lövqvist
Limited Recognition Under 37 C.F.R. 10.9(b)
(see attached)
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 753-6237 (Fax)
Representative of Applicant

ATTACHMENTS:

Exhibit 1: Gaffney et al., Proc Natl Acad Sci USA 1998;95:14875-9.

Exhibit 2: Moser et al., Proc Natl Acad Sci USA 1998;95:14869-74.

Exhibit 3: Tsao et al., J Clin Invest 1997;99:725-31.

Exhibit 4: Tsao et al., J Clin Invest 1999;103:1135-40.